UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,316	12/20/2001	Winston J. Brill	APF 02.05	6832

7590 09/24/2004

PowderJect Pharmaceuticals Plc
Florey House, Oxford Science Park
Oxford, ENG 94555
UNITED KINGDOM

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,316	BRILL ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *4,10,11 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,5-7,9 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A petition under 37 CFR 1.137(b) for revival of an unintentionally abandoned application was received on 5/5/04, and granted on 5/13/04. Prosecution is hereby reopened.

An amendment was received and entered on 5/5/04. Applicant's election without traverse of group 2, claims 5 and 6, is acknowledged. Claims 1-3, 7-9, and 12-15 will be examined to the extent that they are drawn to the claimed invention, i.e. methods of genetically transforming animal cells in vivo in a living animal.

Claims 1-16 remain pending, but claims 4, 10, 11, and 16 are withdrawn from consideration as being drawn to a non-elected invention.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The transmittal letter filled 12/20/01 states that this application is a continuation of 08/352,263, filed 12/7/1994. The '263 application claims priority to Application Nos. 08/148,029 filed 11/05/1993; 07/494,933, filed 3/14/1990; and 07/371,869, filed 6/26/1989. The declaration for patent application filed 12/20/01 claims priority to the '869 application. **However, there is no reference to these applications in the first line of the instant specification, and the applications have no copendency with the instant application.** A reference to the prior application(s) must be inserted as the first sentence of the specification of this application or in an application data sheet (37

CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the

prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

This application claims the benefit of prior filed nonprovisional applications under 35 U.S.C. 120, 121, or 365(c) as discussed above. Copendency between the current application and the prior application is required. However, each of the US applications to which priority is claimed was abandoned prior to the filing date of the instant application (12/20/01). The latest abandonment date was for application serial No. 08/352,263, on 7/24/01. As a result priority is not granted and the effective filing date of the instant application is 12/20/2001.

Specification

The specification is objected to because it lacks a brief description of the drawings.

A substitute specification including the claims is required pursuant to 37 CFR 1.125(a) because the specification and claims currently in the file are photocopies of those from the 08/352,263 priority application, and comprise markings made by PTO clerical staff to indicate the entry of amendments that occurred during the prosecution of that application, e.g. "Insert amendment A". In order to clarify the record, a substitute

specification including the claims is required. A substitute specification must not contain new matter. The substitute specification must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text. Generally, the text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters, and the text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. In this case, because the deleted matter consists of notations made by the PTO clerical staff, it is not necessary (or possible) for Applicant to indicate that these notations were deleted by strike-through or bracketing. Submission of a clean version (without markings) of the specification and a statement that the substitute specification contains no new matter is required.

Oath/Declaration

The declaration for patent application is objected to because the date of the signature of Winston J. Brill is not legible.

The oath is also defective because it fails to list Brian J. Martinell as an inventor. The transmittal letter filed 12/21/01 indicates that the declaration filed therewith is a copy of the declaration filed in Application Serial No. 08/352,263, and that this application is continuation of 08/352,263. However, subsequent to the filing the '263 application, Brian J. Martinell was added as an inventor in the that application, due to

his contribution to the development of the planar carrier sheet, and a subsequent oath was filed which listed Inventors, Brill, McCabe, Yang, and Martinell. Because instant claims 1-9 recite the planar carrier disclosed in the '263 application, but Mr. Martinell is not listed as an inventor in the instant application, the oath is considered to be defective.

Claim Objections

Claims 1-4 and 7-16 are objected to because they are drawn, at least in part, to non-elected inventions. In particular, claims 1-3, 5, 7-9, and 12-15, which are currently under consideration, embrace nonelected subject matter, e.g. methods of transforming cells in vitro (or ex vivo in the case of claims 12-15). Although this Office Action is Non-Final, Applicant is reminded that a complete reply to a final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim 1 is objected to because "animals" at line 25 should be either singular or possessive, and because "particle" at line 26 should be plural.

Claim 2 is objected to because "protein coding" should be hyphenated.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5, 7-9, and 12-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-13 of U.S. Patent No. 5,506,125 Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Instant claims 1, 2, 5, 7-9, and 12-15 are drawn to methods of transforming cells in vivo by use of a device that accelerates toward target cells a carrier sheet layered with nucleic acid-coated microparticles. Motive force is provided by vaporization of a water droplet bridging the gap between two electrodes. Claims 8-13 of '125 are drawn to methods of accelerating carrier particles into a target organism using an apparatus that generates a gaseous shock wave that drives the particles into the organism. The specification describes the apparatus in detail. See e.g. detailed description paragraphs 3 and 4, which disclose the same apparatus as instant paragraphs 11-14. Detailed description paragraph 23 of '125 discusses the use of helium as required by instant claim 8. With regard to the site of delivery, delivery particles, and nucleic acids, '125 teaches that the particles should be used to deliver into somatic cells of a living animal in vivo RNAs or DNA expression constructs encoding proteins and operably linked promoters. See brief description paragraphs 4, 5, 7, 9, and 32. The particles are in a

range of "a fraction to a few microns in size", thereby overlapping the range set forth in instant claim 9. MPEP 2144.05 indicates that in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir. 1990). The specification teaches that the particles can be delivered to somatic cells of the organism. See e.g. detailed description paragraphs 5 and 32.

It is noted that this rejection depends on the specification of the issued patent to describe what is encompassed by the claim terms "acceleration into an organism" and "particles", as well as what is encompassed by the "apparatus" recited in the claims. While the specification of an issued patent generally cannot be used as prior art to support a double patenting rejection, the courts have found that the portion of a patent disclosure which supports the patent claim may be considered when determining double patenting. "[T]his use of the disclosure is not in contrainvention of the cases forbidding its use as prior art, nor is it applying a patent as a reference under 35 USC 103, since only the disclosure of the invention claimed in the patent may be considered." See In re Vogel 422 F.2d 438, 441-42, 164 USPQ 619 (CCPA 1970), and MPEP 804 (II)(B)(1). In this case the disclosure of '125 explicitly supports the organism, particles, and apparatus recited in claims 8-13, such that the claims of' '125 are clearly intended to embrace the subject matter of instant claims 1, 2, 5, 7-9, and 12-15, and a double patenting rejection is required.

Claims 1, 2, 5, 7-9, and 12-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 5,405,779 in view of US Patent 5,506,125.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-9 of '779 are drawn to an apparatus for accelerating carrier particles coated with biological molecules initially loaded onto a carrier sheet into a target organism. The description of the apparatus, i.e. at paragraphs 2-4 of the detailed description matches the essential nature of the apparatus disclosed at detailed description paragraphs 3 and 4 of the '125 patent. There is no restriction of record in the prosecution history.

The '779 patent does not claim a method of transforming somatic cells of a target organism with the claimed apparatus.

The '125 patent teaches the use of an apparatus with the same operating characteristics as the '779 patent for delivery of nucleic acids to somatic cells of an animal (see above). As such it would have been obvious to use the apparatus of the '779 patent to transform somatic cells of an animal.

Claims 1, 2, 5, 7-9, and 12-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,149,655 in view of US Patent 5,506,125.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-10 of '655 are drawn to an apparatus for performing genetic transformation of a living organism in vivo by accelerating carrier particles coated onto a carrier sheet into the organism. The description of the apparatus, i.e. at paragraphs 2-4 of the detailed description matches the essential nature of the apparatus disclosed at detailed description paragraphs 3 and 4 of the '125 patent. There is no restriction of record in the prosecution history.

The '655 patent does not claim a method of transforming somatic cells of a target animal with the claimed apparatus.

The '125 patent teaches the use of an apparatus with the same operating characteristics as the '655 patent, and teaches that it should be used to deliver nucleic acids to somatic cells of an animal (see above). As such it would have been obvious to use the apparatus of the '655 patent to transform somatic cells of a target organism.

Claims 1, 5, and 6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over any one of claims 1-13 of U.S. Patent No. 5,506,125, or claims 1-9 of U.S. Patent No. 5,405,779, or claims 1-10 of U.S. Patent No. 5,149,655, taken with Yang (Crit. Rev. Biotech. 12(4): 335-356, 1992).

The teachings and claims of the '125, '779, and '655 patents are discussed in part above. Additionally, claims 1-7 of '125 are drawn apparatuses for delivering

biological material to cells of a target organism. Each of these references teaches an apparatus for transforming cells by bombardment of the cells with particles coated with nucleic acid, wherein the apparatus comprises a carrier sheet coated with the particles, a spark discharge chamber onto which the carrier sheet is placed, and an electrode gap bridged by a droplet of water which is vaporized by an electrical discharge, as discussed above.

These references do not teach the use of the apparatus to transform skin cells.

Yang teaches the use of an apparatus with the characteristics disclosed in the '125, '779, and '655 patents for delivery of nucleic acids to skin cells. See Fig. 3 on page 345; page 345 column 1, second full paragraph through paragraph bridging pages 345 and 346, especially lines sentence bridging pages 345 and 346. As such it would have been obvious to one of ordinary skill in the art at the time of the invention to use the apparatuses claimed in the a'125, '779, and '655 patents, or the methods claimed in the '125 patent, to transform skin cells as taught by Yang.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-9, and 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 5-9, and 12-15 are indefinite because they recite "the somatic cells" of an animal without proper antecedent basis. The claims are drawn to methods of "genetically transforming the somatic cells of an animal", and could be interpreted as requiring transformation of each and every somatic cell of the animal, or as requiring the transformation of a subset of the somatic cells of the animal. MPEP 2173.02 states that definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;
(B) The teachings of the prior art; and
(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In view of the specification as a whole, the claimed method is not interpreted as a method of transforming every somatic cell in an organism, instead it is directed to transforming a fraction of those cells. See e.g. paragraph 5, which states in part that the "invention is directed toward a method of transforming the somatic cells of animals in vivo in which ... the particles are accelerated at the target and into the cells of the target animal to thereby **genetically transform a portion of the cells so treated** so as to transform in vivo in the animal a number of cells to produce the protein coded by the exogenous gene. Emphasis added. The specification never explicitly indicates that the claimed method is directed toward transforming every cell in an organism, and the state of the art at the time of the invention was such that the skilled artisan would not expect any technique for gene delivery to somatic cells in vivo to result in delivery to every somatic cell in an animal. Given the teachings of specification as a whole, and the state of the art at the time of the invention, one of ordinary skill in the art would not reasonably interpret the claims as methods of transfecting all somatic cells in an

organism. Because the claims, when read in light of the specification, do not require transformation of each and every somatic cell in an organism, one of skill in the art is left to ask which somatic cells does Applicant intend by "the somatic cells", and the claims are indefinite for lack of antecedent basis. It is suggested that the article "the" should be deleted in the phrase "the somatic cells".

Claims 1-3, 5-9, and 12-15 are indefinite because they recite "the animal cells" (e.g. at lines 6, 8, 9, 17, 23, 24, 25, 26, and 30 of claim 1), "the cells" (e.g. at lines 6 and 30 of claim 1), and "the cells of the animal" (e.g. at line 6 of claim 12) without proper antecedent basis. It is suggested that "said somatic cells" should be substituted for each of these phrases throughout the claims.

Claims 1-3, 5-8, and 12-15 are indefinite because they recite the term "dense", which is a relative term. The term "dense" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "dense" limits the nature of material from which carrier particles are made, so one of skill in the art cannot know what materials infringe the claims.

Claims 1-3 and 5-8 are indefinite because the metes and bounds of "a size very small in relation to the size of the animal cells" are unclear. This passage relates to the size of particles used to bombard animal cells. Although the specification teaches at paragraph 5 that the particles should be of a size that does not disrupt the biological function of the cells into which they are propelled, it is unclear if the phrase "very small" is intended to reflect this requirement, or is intended to limit the size of the particles

even further, or perhaps in some other way. As a result, it is unclear what range of sizes infringes the claims. Furthermore, there is no nexus between the somatic cells to be transformed, and "the animal cells" that are the reference for the size of the particles. Animal cells come in a variety of sizes including cuboidal epithelial cells that are a few hundred microns in diameter to spinal neurons that can be a meter in length and which vary widely in diameter depending on the location in the cell. As a result, the claims recite "the size" without proper antecedent basis.

Claims 1-3 and 5-9 are indefinite because they recite "the direction of travel of the carrier sheet" without antecedent basis. After reading the claim as a whole, it is not clear that the carrier sheet is limited to any one direction of travel. As such, one of skill in the art cannot know in which direction the animal cells must be placed. It is suggested that "in the direction of travel of the carrier sheet" should be deleted, and the claims should require placement of the somatic cells on the opposite side of the carrier sheet from the spark discharge chamber.

Claims 1-3 and 5-9 are indefinite in their recitation of the relative term "high". The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "high" is used to limit the parameter of "voltage". Although the claim requires that the amount of voltage used must cause a spark to bridge the gap between two electrodes, it is not clear that "high" voltage is required for this to happen. As a result one of skill in the art cannot know what amount of voltage infringes the claims.

Claims 1-3 and 5-9 are indefinite in their recitation of the relative term "minimal". The term "minimal" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "minimal" is used to limit the parameter of "damage". As a result one of skill in the art cannot know what amount of damage infringes the claims.

Claim 8 is indefinite because it recites "the area" without proper antecedent basis. Substitution of "an" for "the" is suggested.

Claims 12-15 are indefinite because it is unclear what are the metes and bounds of "small in size relative to the size of the cells of the animal". Specifically, it is unclear what range of sizes is embraced. The term "small" is a relative term that is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Although the specification teaches at paragraph 5 that the particles should be of a size that does not disrupt the biological function of the cells into which they are propelled, it is unclear if the term "small" is intended to reflect this requirement, or is intended to further limit the size of the particles. As such one of skill in the art cannot know the metes and bounds of the claims. Also, animal cells come in a variety of sizes including cuboidal epithelial cells that are a few hundred microns in diameter to spinal neurons that can be a meter in length and which vary widely in diameter depending on the location in the cell. As a result, the claims recite "the size" without proper antecedent basis.

Claims 12-15 are indefinite because they recite "the flow" and "the electrical discharge" without proper antecedent basis. See line11 of claim 12. There is no nexus between the electrical potential recited in line 10, and the electrical discharge in line 11, so the electrical potential does not provide an antecedent for the electrical discharge. In fact, the claim as written does not require the vaporization of a water droplet, or even the presence of a water droplet in the apparatus. Instead it requires only the use of an electrical discharge to accelerate the coated carrier by any means without limitation, so long as the means uses a force equal to that of the expanding vapor of a water droplet vaporized by an electrical potential.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-3 and 5-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 3 is explicitly drawn to the genus of DNA sequences effective to express a negative strand RNA in an animal cells to inhibit disease processes. The genus of disease processes is extremely broad and includes such diverse diseases processes as

bacterial infection, heart disease, and Alzheimer's disease. The specification fails to adequately describe the claimed genus of DNA sequences because it fails to describe a single species of the genus by reduction to practice, complete structure, or relevant identifying characteristics. Claim 3 depends from claim 1, so claim 1 also embraces this genus and is included in the rejection. Claims 2 and 5-9 depend from claim 1, These claims do not exclude the genus and are included in the rejection as well for that reason.

Enablement

Claims 1-3, 5-9, and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of genetically transforming somatic cells of an animal at a site on the animal that is contacted with carrier particles coated with a genetic construct for expressing a protein of interest, does not reasonably provide enablement for methods of genetically transforming somatic cells distal to the site of administration, or for methods of inhibiting disease processes or gene expression in vivo by expression of negative strand RNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-3, 5-9, and 12-15 are directed to methods of "genetically transforming the somatic cells of an animal". The scope of "the somatic cells of an animal" is not limited cells specifically at the site of administration. As a result, claims 1-3, 5-9, and 12-15 can be reasonably interpreted as embracing embodiments ranging from

transforming somatic cells at the site of administration to transforming somatic cells distal to the site of administration.

The specification teaches working examples of the delivery of reporter genes, but does not determine the amount or percentage of cells transformed in vivo. However, the specification does show that, when performed on cells in vitro in culture, the method allowed a transformation efficiency of 5.2-6.4 X 10^{-4}, or about 0.06%. See e.g. page 11, lines 15-22. So it is clear that not all cells at the site of administration are transformed. The specification provides no guidance as to how to improve this efficiency such that cells are transfected in regions distal to administration, and there is no apparent reason why any cells distal to the site of administration should become transformed because the delivery is targeted at the site of particle administration. Because the specification provides no guidance as to how to use the method to achieve transformation of somatic cells other than at the site of administration, because no such guidance is available in the prior art of record, and because there is no logical reason to expect that such transformation would occur using the claimed method, one of skill in the art would have to perform undue experimentation in order to use the claimed method to transform somatic cells in an organism other than at the site of administration.

Claim 3 depends from claim 1 and is drawn to a method of using negative strand RNA to inhibit "a native gene" of a somatic cell in vivo, or alternatively to inhibit "disease processes". The phrase "inhibit a native gene" is interpreted for the purpose of this analysis as "suppressing the expression of a gene of said somatic cell". The specification teaches no specific purpose for suppressing native gene expression. The

phrase "disease processes" is not defined by the specification, and is given its broadest reasonable interpretation. As such the claim embraces methods ranging from those resulting in therapeutic benefit to cure. The range of diseases and disease processes is not limited and would include such varied diseases as bacterial and viral infections, heart disease, cystic fibrosis, muscular dystrophy, and Alzheimer's.

The specification teaches that the claimed invention can be used to transform somatic cells of an animal with a genetic construct encoding a protein of interest (see page 5, lines 10-22. It was recognized in the art prior to the time of the invention that particle bombardment could be used for this purpose. For example, Suter et al (Proc. Nat. Acad. Sci. USA 96(22) : 12697-12702, 1999) taught the use of particle bombardment for genetic immunization. See abstract. Also, Yang (Crit. Rev. Biotech. 12(4): 335-356, 1992) taught that an apparatus identical to the one described in the instant claims could be used to assay in vivo the promoter performance of expression constructs, and for genetic immunization. See Fig. 3 on page 345, and page 346, paragraph bridging columns 1 and 2, and column 2, first full paragraph.

However, at the time of the invention, the state of the art in antisense inhibition was such that one of skill in the art could not routinely and predictably inhibit in vivo gene expression or disease processes as broadly and generally claimed. The state of the art with respect to antisense therapies indicates a high level of unpredictability. Crook (In Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, pgs. 1 and 4), teaches that although antisense techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable (pg. 1,

Introduction). Crook points out several factors which may influence the biological effect of an antisense sequence including the rate of distribution within the target cell, stability within the target cell, local concentration of the sequence, and the concentration and stability of the target mRNA (pgs. 1 and 4). Furthermore, Branch (Trends in Biochem Sci 23: 45-50, 1998) teaches that selection of appropriate antisense sequences for use in vivo is difficult because secondary structures of mRNAs *in vivo* frequently restrict access of antisense sequences to the target sequence (page 45, col. 3. first para., page 48, last para. and page 49). Branch states, "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49, col. 2, last para.). Ho and Parkinson (Sem. Drug Discov. 24(2): 187-202, 1997) teach that although antisense therapy is simple in theory, it "has proven to be much more complex in practice. A number of important challenges in the preclinical development of antisense sequences have been identified, including stability, sequence length, cellular uptake, target sequence selection, appropriate negative controls, oligonucleotide: protein interactions, and cost of manufacture." The authors conclude that "[c]ontinued progress in this arena will require that many of the preclinical challenges confronting antisense development are satisfactorily resolved." See abstract. Akhtar (J. Antimicrob. Chemother. 38(2): 159-165, 1996) teaches that a healthy degree of concern exists among scientists and administrators as to whether antisense will ever become useful therapeutic agents." See page 163, column 1, lines 5-14 of first full paragraph. Thus, at the time the invention was made, there was considerable unpredictability in the design of inhibitory antisense sequences, their pharmacodynamics, and most importantly, whether or not

they would ultimately have use in vivo. As a result it is extremely unpredictable as to whether or not one could use the claimed invention to inhibit native genes in vivo, or to inhibit disease processes by inhibiting genes expression of genes involved in those processes.

The instant invention addresses aspects of gene delivery, but specific guidance with regard to the use of antisense sequences is limited to a single sentence fragment, i.e.

> "the inserted construction could express a negative RNA strand effective either to suppress the expression of a native gene or to inhibit a disease pathology."

The specification teaches no working example of suppression of gene expression or of inhibition of any disease process. It provides no guidance at all with regard to the design of antisense sequences. It fails to disclose a single sequence that can be used to inhibit expression of any gene or to inhibit any disease process. It does not disclose any gene associated with any disease process or any specific disease or disease process that can be inhibited. For example, it is unclear as to how an infection by a bacterium that replicates extracellularly could be affected by the delivery to somatic cells of the infected organism of an antisense expression construct. The specification fails to teach what somatic cell gene should be inhibited to affect the process of bacterial infection. The specification also fails to teach how to affect the processes of diseases cause by loss of function mutations. For example, cystic fibrosis is caused by a loss of function in the cystic fibrosis transmembrane conductance regulator, an ion channel that regulates cellular sodium and chloride ion flux. The specification fails to teach how to affect any process associated with cystic fibrosis, particularly ion flux, by

delivery of any antisense expression construct. One might argue that these disease processes include aspects such as inflammation, and that one could affect them by transforming cells with antisense expression constructs that inhibit genes required for inflammation. However, the specification has failed to identify a single gene that is involved in that, or any other disease process. Setting aside the issue of unpredictability of antisense therapy, the court has recognized that while Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the claimed invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the diseases processes that can be inhibited, the genes related to these processes, and the RNA sequences that can be used to inhibit gene expression or disease processes, are not minor details that can be omitted in the process of providing an enabling disclosure. As such, and in view of the unpredictability in the art and the

low frequency of gene delivery obtained by the method as discussed above, one of skill in the art could not use the claimed invention for the inhibition of native genes or disease processes in vivo as broadly claimed without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1-3, 5-9, and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Brill et al (WO 91/00359, published 1/10/1991).

Claims 1-3, 5-9, and 12-15 of Brill are identical to instant claims 1-3, 5-9, and 12-15.

Thus Brill anticipates the claims.

Claims 1, 2, 5, 7-9, and 12-15 are rejected under 35 U.S.C. 102(b) and 102(e) as being anticipated by McCabe et al (US Patent 5,506,125, issued 4/9/1996).

McCabe teaches an apparatus for genetically transforming somatic cells of an animal as required by the claims. See brief summary paragraph 6; detailed description paragraphs 3 and 4 which provide a general description of the apparatus and its use, and detailed description paragraph 23 which discusses the use of helium as required by instant claim 8. McCabe also teaches that the apparatus should be used to deliver DNA expression constructs encoding proteins and operably linked promoters, or RNAs, into cells of a living animal in vivo. See brief description paragraphs 4, 5, 7, and 9. The expression constructs are coated onto gold particles in a range of "a fraction to a few microns in size", thereby overlapping the range set forth in instant claim 9. MPEP 2131.03 addresses the situation wherein the prior art range overlaps the claimed rage but no specific examples are disclosed that fall within the claimed range. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. In this case, there is no evidence of unexpected results, and the phrase "a fraction to a few microns in size" does not constitute a "broad" range relative to the claimed range of 1-3 microns.

Thus McCabe anticipates the claims.

Claims 1, 2, 5, 7-9, and 12-15 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Because the instant application is currently unassigned and has a different inventive entity than does the McCabe patent, the claims are also rejected under 35 USC 102(f) because it is not clear who invented the claimed subject matter. See MPEP 804, page 800-16, 800-25, and 800-26, available at: http://www.uspto.gov/web/offices/pac/mpep/mpep_e8_0800_508.pdf.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5, 7-9, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,405,779 in view of US Patent 5,506,125 (McCabe).

Claims 1-9 of '779 are drawn to an apparatus for accelerating carrier particles coated with biological molecules initially loaded onto a carrier sheet into a target organism. The description of the apparatus, i.e. at paragraphs 2-4 of the detailed description matches the essential nature of the apparatus disclosed at detailed description paragraphs 3 and 4 of '125. There is no restriction of record in the prosecution history.

The '779 patent does not claim a method of transforming somatic cells of a target organism with the claimed apparatus.

McCabe teaches the use of an apparatus with the same operating characteristics as the '779 patent, and teaches that it should be used to deliver nucleic acids to somatic cells. See brief summary paragraph 6; detailed description paragraphs 3 and 4 which provide a general description of the apparatus and its use, and detailed description paragraph 23 which discusses the use of helium as required by instant claim 8. McCabe also teaches that the apparatus should be used to deliver DNA expression constructs encoding proteins and operably linked promoters, or RNAs, into cells of a living animal in vivo. See brief description paragraphs 4, 5, 7, and 9. The expression constructs are coated onto gold particles in a range of "a fraction to a few microns in size", thereby overlapping the range set forth in instant claim 9. MPEP 2131.03 addresses the situation wherein the prior art range overlaps the claimed rage but no specific examples are disclosed that fall within the claimed range. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. In this case, there is no evidence of unexpected results,

and the phrase "a fraction to a few microns in size" does not constitute a "broad" range relative to the claimed range of 1-3 microns.

As such it would have been obvious to use the apparatus of the '779 patent to transform somatic cells of a target organism.

Claims 1, 2, 5, 7-9, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,149,655 in view of US Patent 5,506,125 (McCabe).

Claims 1-10 of '655 are drawn to an apparatus for performing genetic transformation of a living organism in vivo by accelerating carrier particles coated onto a carrier sheet into the organism. The description of the apparatus, i.e. at paragraphs 2-4 of the detailed description matches the essential nature of the apparatus disclosed at detailed description paragraphs 3 and 4 of '125. There is no restriction of record in the prosecution history.

The '655 patent does not claim a method of transforming somatic cells of a target organism with the claimed apparatus.

McCabe teaches the use of an apparatus with the same operating characteristics as the '779 patent, and teaches that it should be used to deliver nucleic acids to somatic cells. See brief summary paragraph 6; detailed description paragraphs 3 and 4 which provide a general description of the apparatus and its use, and detailed description paragraph 23 which discusses the use of helium as required by instant claim 8. McCabe also teaches that the apparatus should be used to deliver DNA expression

constructs encoding proteins and operably linked promoters, or RNAs, into cells of a living animal in vivo. See brief description paragraphs 4, 5, 7, and 9. The expression constructs are coated onto gold particles in a range of "a fraction to a few microns in size", thereby overlapping the range set forth in instant claim 9. MPEP 2131.03 addresses the situation wherein the prior art range overlaps the claimed rage but no specific examples are disclosed that fall within the claimed range. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. In this case, there is no evidence of unexpected results, and the phrase "a fraction to a few microns in size" does not constitute a "broad" range relative to the claimed range of 1-3 microns.

As such it would have been obvious to use the apparatus of the '655 patent to transform somatic cells of a target organism.

Claims 1, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of U.S. Patent No. 5,506,125, or U.S. Patent No. 5,405,779, or U.S. Patent No. 5,149,655, when taken with Yang (Crit. Rev. Biotech. 12(4): 335-356, 1992).

The teachings and claims of the '125, '779, and '655 patents are discussed in part above. Each of these references teaches an apparatus for transforming cells by bombardment of the cells with particles coated with nucleic acid, wherein the apparatus comprises a carrier sheet coated with the particles, a spark discharge chamber onto which the carrier sheet is placed, and an electrode gap bridged by a droplet of water which is vaporized by an electrical discharge, as discussed above.

These references do not teach the use of the apparatus to transform skin cells.

Yang teaches the use of an apparatus with the characteristics disclosed in the '125, '779, and '655 patents for delivery of nucleic acids to skin cells. See Fig. 3 on page 345; page 345 column 1, second full paragraph through paragraph bridging pages 345 and 346, especially lines sentence bridging pages 345 and 346. As such it would have been obvious to one of ordinary skill in the art at the time of the invention to use the apparatuses claimed in the a'125, '779, and '655 patents, or the methods claimed in the '125 patent, to transform skin cells as taught by Yang.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.